Original Research Paper

Volume - 12 | Issue - 09 | September - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Psychiatry

NEUROPSYCHIATRIC SEQUELAE AND TRAUMATIC BRAIN INJURY (TBI)

Dr Kritika Agarwal	Junior Resident, Department of Psychiatry, Lady Hardinge Medical College, New Delhi.
Dr Saurabh	Senior Resident, Department of Psychiatry, Lady Hardinge Medical College, New Delhi.
Dr Nileshwar Das	Senior Resident, Department of Psychiatry, Lady Hardinge Medical College, New Delhi.
Dr Dinesh Kataria	Director Professor and HOD, Department of Psychiatry, Lady Hardinge Medical College, New Delhi.
Dr Prerna Kukreti	Associate Professor, Department of Psychiatry, Lady Hardinge Medical College, New Delhi.
Dr Saloni Seth*	Junior Resident, Department of Psychiatry, Lady Hardinge Medical College, New Delhi. *Corresponding Author

KEYWORDS :

1. INTRODUCTION

TBI has been named the **"Silent Epidemic"** because of the limited knowledge about the issue, and of its symptoms such as memory and cognitive problems, which may not be immediately evident (*Headway, UK National head Injury Association)*. TBI refers to "an acquired injury to the brain caused by an external physical force, resulting in total or partial functional disability or psychosocial impairment, or both, that adversely affects an individual's performance. Alteration in brain function can be caused by an injury from a blow, jolt, or a penetrating object *(International Brain Injury Association)*.

Classification of Traumatic brain injury:

1) Depending on the time of occurrence of injury:

TBI is classified into primary and secondary brain injury.

The injury which occurs at the time of incident of contact or inertia force is called primary injury. Contact forces may cause laceration, skull fracture, intracranial haemorrhage, contusions, and intracerebral haemorrhage. Acceleration and/or deceleration and rotational forces constitute inertial loading forces which results in diffuse axonal injury and acute subdural hematoma from the subdural bridging veins.

The brain damage that happens by pathological processes that start at the time of injury, but span a variable period following the traumatic event is called secondary injury. This constitutes brain damage secondary to ischaemia which has resulted from hypotension , hypoxia, brain swelling, raised intracranial pressure and infection.

2) Depending upon the integrity of meningeal coverings:

TBI is classified into closed (non-penetrating) and open (penetrating) injuries.

3) Depending upon the extent of brain area involved:

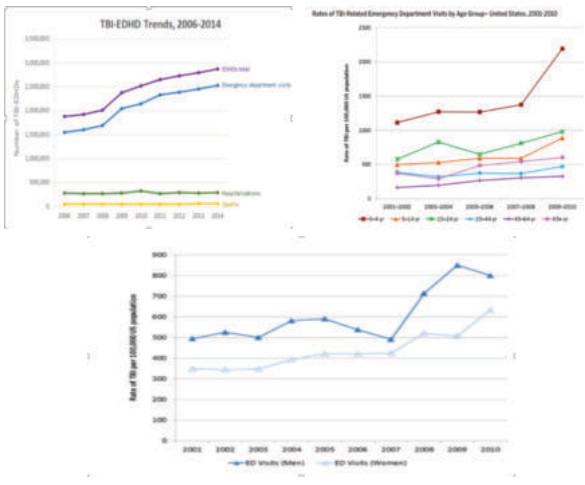
TBI is classified into focal lesions and diffuse lesions.

Focal lesions consist of contusion, lacerations, intracranial-extracerebral haemorrhage, and focal ischaemic lesions. Diffuse lesions include traumatic axonal injury (which occurs mostly within corpus callosum, thalamus and dorsolateral quadrants of the upper brainstem) and diffuse ischaemic damage.*(Comprehensive Textbook of Psychiatry 10th Edition)*

2. Epidemiology

According to the *Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2016*, there were 27.08 million (95% uncertainty interval [UI] 24.30 – 30.30 million) new cases of TBI, with age-standardised incidence rates of 369 (331 - 412) per 100,000 population for TBI. This has increased by 3.6% from the year 1990 till 2016. The prevalence rate was 55.50 million (53.40-57.62 million) which has increased by 8.4% from the year 1990. TBI caused 8.1 million (95% UI 6.0-10.4 million) Years lost due to disability (YLD) in 2016, corresponding to age-standardised rates of 111 (82-141) per 100,000. Annual global economic burden due to TBI was estimated be USD 400 Billion.

In high income countries, there were approximately 2.87 million TBI-related emergency department, hospitalizations and death (EDHDs). The number of total TBI-EDHDs increased by 53% from 2006 to 2014. For each year, 2001 - 2010, men had higher rates of TBI-related ED visits compared to women. From 2007 – 2010, there was a striking increase in rates among both men and women with higher increase in the rate among men compared to women. Rates of TBI-related ED visits increased for all age groups from the period of 2001–2002 through 2009–2010. The rates of TBI-related ED visits increased the most for youth under four years of age. From 2007-2008 to 2009-2010, the rates of TBI-related ED visits in this group increased by more than 50% from 1,374.0 to 2,193.8 per 100,000 *(TBI Data and Statistics, CDC Injury Center, 2015)*



TBI has reached epidemic proportions in India and shares the main causes of acquired brain injury along with stroke *(Kamalakannan et al, 2015)*. It is regarded as a predominant public health concern in India. Rapid urbanization, economic growth and lifestyle changes are the main reasons for this increase in the burden in India *(Gururaj G et al, 2005)*. Every year around 1.5 to 2 million individuals are injured and 1 million succumb to death in India. Road traffic accidents (55.5%) and falls (29.2%) were the most commonly reported causes of injury for TBI in India, compared to developed countries, where getting struck

by or against an object and falls accounted for a majority of the injuries. *(Gururaj et al. 2002)*

3. Pathophysiology

TBI begins with the initial brain trauma i.e. the primary brain injury which causes mechanical damage and results in disruption of the Blood Brain Barrier (BBB); alteration of the vasculature and injury to neurons and glial cells *(Kigerl et al 2014; Dinarello et al. 2007)*. Injured neurons and glial cell releases DAMP (Damaged Associated Molecular Pattern) into the extracellular space which in turn activates surrounding cells. Activated cells then generate molecular signals that exacerbate or resolve the acute injury.

Secondary injury follows it which involves an influx of peripheral inflammatory cells through the disrupted BBB leading to release of reactive oxygen species, cytokines, chemokines, and free radicals. Ion imbalance across the cell membrane causes release of excitatory neurotransmitter, increase in the Ca2+ concentration activates protease, lipase all these changes leads to cell disruption and eventually neuronal death (Werner C et al, 2007; Miller AH et al, 2013)

4.Risk Factors Influencing Psychiatric Sequelae After Tbi

Neuropsychiatric disorders are one of the most frequent and disabling complications of TBI. The severity of psychiatric sequelae of TBI is determined by several factors. For better clarity, it is divided into environmental, personal, medical and scale determining factors.

ENVIROMENTAL	PERSONAL	MEDICAL	SCALE MEASURES
Mechanism of injury	Age, Gender	Anaemia Arteriosclerosis	Low score in MINI Unfavourable outcome in Glasgow Outcome Scale
Type and severity of injury	Genetic-Apolipoprotein status	Endocrine complication	-
Location of injury	Premorbid personality Premorbid psychiatric illness Premorbid behaviour disturbances	Physical and cognitive handicap Neurological disorder	-
Deployment stressor	Cognitive reserve	-	-
Disability supports	-	-	-
Social supports	-	-	-
Compensation and litigation issues	-	-	-

A study by *Fann JR et al. 2004* compared the occurrence of psychiatric disorders between 939 patients with TBI and 2817 controls. The prevalence of any psychiatric illness in the first year was 49% following moderate-severe TBI compared to 34% following Mild TBI and 18% in the control group.

Among patients without a history of psychiatric illness, the adjusted related risk of any psychiatric illness following 6 months of moderate-severe TBI was 4.0 and following mild TBI was 2.8 compared with those without TBI. Among patients with previous psychiatric disorder, the adjusted relative risk of any psychiatric illness in moderate-severe case was 2.1 and following mild TBI was 1.6. It showed that prior psychiatric illness is a strong predictor of psychiatric morbidity following TBI and further that the rate of psychiatric illness is higher following TBI compared to the control group even (several) years after TBI.

5. Acute Psychiatric Sequelae

There is an overlap in the emergence and progression of symptoms following TBI. Impairment of consciousness is the most consistent of the acute effects of head injury *(Brian J Blith et al, 2010)*. It ranges from momentary dazing to prolonged coma. Loss of consciousness (LOC) usually follows after rotational injury, rare in static and penetrating injuries. Longer the duration of LOC, more is the probability of permanent damage. *(Schiff et al, 2010)*

During recovery from impaired consciousness, patients go through a phase of post traumatic delirium. Around two thirds of the patients who survived TBI develop agitation and delirium *(Ganau et al, 2018)*. It has a multifaceted symptom complex characterised by a confused state, fluctuating mental status and attention, disorganised thinking, altered level of consciousness, acute onset motor signs, hallucinations, disorientation for time and place is marked, and sleep abnormality. It was seen in a study by *Maneewong et al 2017* that almost of patients with mild to moderate head injuries develop delirium within first 4 days following TBI. Patients having low GCS score (especially verbal component score), cognitive impairment, sleep- wake disturbance were more likely to have delirium in this period. It was seen incidence and duration of PTD is higher than delirium in non-TBI ICU patients *(Gnau et al. 2018)*.

Post traumatic agitation can accompany delirium during the recovery phase. Excitable and overactive phase with florid disturbance of behaviour are usual features seen in post-traumatic agitated patients. It can occur as a result of delusion, hallucination, changes of temperament and behaviour. Around 25% of patients with TBI were classified as being aggressive during the follow-up periods *(Baguley et al. 2006)*. Majority resolve spontaneously within a few weeks. It was found that post traumatic agitation doubles the risk of emotional sequelae in later Stage.

Post-traumatic amnesia is a state of confusion that occurs immediately following TBI. It is the amnesic gap from the moment of injury to the time of resumption of normal continuous memory *(Lishman's Organic Psychiatry)*. Delayed onset of PTA is seen in extradural haemorrhage. It can be retrograde or anterograde. Confabulations may be evident during this phase to fill the amnesic gap. Deficits in declarative memory are common, procedural memory is usually spared. Duration of PTA is a good predictor of degree of disability, vocational outcome and severity of personality change *(Eastvold et al, 2012)*. It can last for more than a month in more than 45% patients following TBI (*Tessa Hart et al. 2016*) Retrograde amnesia is the duration between the moment of injury and the last clear memory from before the injury can be recalled. Long duration is seen in severe injury due to *hypoactivation of an area of right frontal lobe, Anterior cingulate gyrus Hippocampus (Bright et al. 2012)*. Final estimate of the duration of retrograde amnesia should be made only after resolution of PTA and fullest possible regain of cortical function.

6. Chronic Psychiatric Sequelae

6.1 Cognitive Deficit

Cognitive functions are specific mental functions especially dependent on the frontal lobes of the brain, including complex goal-directed behaviors. Cognitive dysfunction alters a patient's ability to perform activities of daily living. Relationship between acute TBI severity and cognitive sequelae is approximately linear *(Rabinowitz et al, 2014)*. Cognitive changes are more closely associated with long-term disability as compared to sensory and motor deficits *(Giannouli et al. 2018)*. Memory, attention, processing speed, executive functioning domains are affected in mild TBI in addition to these domains in moderate to severe TBI communication, visuospatial processing, intellectual ability, awareness of deficits are also affected. It was seen in several studies that cognitive dysfunction resolves rapidly within 80%-85% patients and may persist in 15% of patients following mild TBI while in moderate-severe cases it persists in 65% cases *(Belanger et al, 2005, Frenchman 2005, Schretelen DJ 2003, Pagulayan et al. 2007)*.

6.2 Memory

This is the most frequent dysfunctions and complaints in chronic phase following TBI. It may be acute or chronic. Acute memory disturbances are seen in post-traumatic amnesia and post-concussion syndrome, generally time-limited and resolve within a week. Deficits in medial temporal lobe processing (particularly hippocampal and/or amygdaloid) is found in memory disturbances cases *(Mckee et al, 2015)*. Main problem lies in difficulty encoding or retrieving recent memory. Memory disturbance is seen in post TBI patients differs from amnestic memory disorder by having difficulty in organization of memory encoding unlike amnestic memory disorder there is no storage deficit. *(Vanderploeg et al, 2014)*

6.3 Executive Functioning

Executive functioning disturbances are common following TBI, even among those with mild injuries. It threatens an individual's ability to engage successfully in independent goal-oriented behavior. It is critically important for the quality of life (*job performance, social relationships, and both basic and instrumental activities of daily*

living). Executive deficits are more predictive of functional disability than demographic and injury variables *(Rabinowitz et al. 2014.Dikmenn SS et al, 2009).*

FOLLOWING ARE THE EXECUTIVE FUNCTIONS AFFECTED IN TBI *(Amanda R et al, 2014)*

Cognitive executive functions	Behaviours executive functions
• Memory Acquisition and Retrieval • Top-down Control of attention • Planning • Judgement • Cognitive Aspects Decision making	• Emotional aspects of decision making • Motivation • Impulsivity

6.4 Depression

It is one of the most common sequelae in TBI survivors. Incidence rates of depression vary from 15.3%- 33% in different studies. Lack of energy, difficulty in concentration and irritability are predominant depressive symptoms prevalent in patients underwent TBI *(Schwartzbold et al 2008)*. In a study by *Jorge et al. 2004 (6 month follow up study)* 33% were depressed post TBI compared to 7.4% in post non-cranial traumatic group. Risk of depression is highest in 1st year following TBI. Women found to be more depressed in 1st 6 months as compared to male. However no persistent gender difference found at 1 year postinjury *(Lavoie et al, 2017)*. Anxiety, substance misuse and behavioural alterations like impulsivity and aggression are frequent comorbidities found to be associated with post TBI depression

Relation between depression post TBI and specific brain regions: *(Jorge et al 2005, Fedroff et al 1992, Paradiso et al 1999, Rola et al 2006)*

- Left prefrontal grey matter volume reduction *(especially in ventrolateral and dorsolateral region)*
- *Left basal ganglia in acute phase of TBI*
- *more severe depression in Lateral frontal lobe lesions as compared to medial lesion*
- *Anterior temporal regions*
- *Alteration of Hippocampus neurogenesis and gliogenesis.*

6.5 Mania

Mania is observed less commonly following TBI compared to depression. Frequency of secondary mania varies from 1.7% to 9.0% *(Silver et al, 2001; Van Reekum et al, 2000)*. Premorbid TBI was associated with a higher YMRS disruptive component score (OR 1.7, 95% CI 1.1–2.4, p=0.0077) and more comorbid migraine (OR 4.6, 95% CI 1.9–11, p=0.00090). Episodes of mania in post TBI cases are short lasting characterised by more aggression, irritable mood, and less euphoria *(Drange OK et al, 2018)*. Items on disruptive, aggressive behavior and irritability had the highest loadings on the YMRS disruptive component. According to a study by *Chi et al 2016* one in ten diagnosed with bipolar disorder (BD) has experienced a premorbid traumatic brain injury. *Associated seizure is present in 50% patients with mania developed after TBI.* Gender difference was also observed significantly in this condition 1 out of 10 female developed mania compared to 4 of 8 males *(Van Reekum et al, 1996)* Relation between mania post TBI and specific brain regions (Jorge RE 1993, Starkeistein et al 1988)

- *Left Temporal basal poles*
- *Orbitofrontal cortex mainly right side*
- *Right limbic system*
- *Anterior subcortical atrophy*

6.6 Post Traumatic Stress Disorder

Frequency of PTSD depends upon the severity of brain injury in mild TBI cases frequency was found to be 12%-30% *(Bryant et al, 2010; Hibbard et al 1998; Wei W et al, 2005)* while in Moderate TBI cases 15-27% and severe TBI 3-23% *(McCauley et al, 2001, Glaesser J et L 2004)*. Its association with acute stress disorder (ASD) was assessed by Bryant et al. It was found that 81.8% of ASD cases developed PTSD compared to 11.5% in non ASD (Cahill et al, 2005). PTSD with TBI has more severe symptoms as compared to PTSD alone *(Bryant et al, 2011)*. TBI is associated with a greater risk of developing PTSD compared with other bodily injuries. Presence of memory of the event within the first 24 hours is a strong predictor of PTSD. It was seen that 27% of conscious patient at the time of injury developed PTSD compared to 3% among unconscious *(Glaesser et al, 2004)*. High frequency of heart rate was found to be predictor of PTSD *(Shah et al, 2015).* S 100 B in the acute phase also observed as a predictor of PTSD *(Sojka et al, 2006)*. Self-reported diagnostic have limited use due to overlapping symptoms. Rate of PTSD was 40% using self-reported questionnaire while using structured interview it was found to be 3%

6.7 Change Of Personality

Alteration in habitual attitude and behaviour which is different from before is observed after TBI. It results from direct disturbances of neural tissue, or due to indirect effects of the brain injury such as reactions and responses to impairments, environmental factors, premorbid personality. 23.3% had at least one personality disorder. Most common being avoidant (15.0%), paranoid (8.3%), and schizoid (6.7%) personality disorders *(Koponen et al, 2002).* Three main variants of frontally mediated changes in personality described by Luria are dysexecutive, pseudo depressed characterized by apathy, indifference, decreased initiative, inflexibility, and perseveration and pseudo psychopathic syndrome manifests with disinhibition, antisocial behavior, affective lability, hyperactivity, impulsivity. In Temporal lobe lesions features of epileptic personality change such as Circumstantiality; viscosity are seen. In Basal syndrome (Injury to basal structures like midbrain/ hypothalamus apathy, lability are observed. Personality change are common in patients with abnormal EEG or compressed ventricles on early CT scan.

6.8 Psychosis

It is classified in Psychotic disorder caused by another medical condition in DSM 5. It is a rare but severe outcome of traumatic brain injury. Prevalence rate varies from 0.9% to 8.5% *(Chen YH et al, 2011; Fann JR et al 2002; Harrison et al, 2006)* . Psychotic disorder seen post TBI are categorised into Delusional disorder and Schizophrenia like psychosis. No strong relationship between severity of TBI and onset of psychosis was observed. There is a bimodal distribution of time between TBI and onset of psychosis. Male gender and family history of schizophrenia are risk factors for developing psychotic disorder post TBI. Negative symptoms are less pronounced in people with psychotic disorder which develops after TBI *(Fujii et al, 2012).* PD-TBI is associated with lesions to frontal and temporal areas of brain as identified by neurological studies. Seizure disorder is more common in psychotic disorder associated with TBI than in general TBI.

6.9 Post Concussion Syndrome

It is a syndrome usually follows head trauma with LOC characterised by Headache, dizziness, irritability, fatigue, insomnia and memory impairment. Though any severity of TBI can cause PCS; Mild TBI is more prone to cause post-concussion syndrome *(Permenter et al, 2020*).

6.10 Dissociative (Conversion) symptoms

Fits, fugues, amnesia, Ganser states, paralysis, anesthesia, and disturbance of speech, sight or hearing are common dissociative symptoms. Among 21% patients with dissociative disorder give past history of TBI within 6months. Neurasthenic reaction may incapacitate the patient for months or even years (Whitlock, 1967)

6.11 Post Tbi Headache

It is very common in acute phase of TBI usually resolves in a few days; however, some patients report prolonged headache after TBI. It may persist for many years with poor response to analgesics. Severe post TBI headache should raise the suspicion of Chronic SDH (Ashina et al, 2019)

6.12 Tbi & Epilepsy

Post TBI epilepsy develops in around 5% of closed injuries and around 30% in penetrating injuries (Ding et al, 2016). TBI can also be secondary to epilepsy. Closed head injury is generally associated with Temporal lobe epilepsy. Severity of TBI also plays role in causing epilepsy. Contusions are more prone to cause epilepsy. Cortical scarring due to contusions are highly epileptogenic.

8. Management Of Psychiatric Sequelae Following Tbi

Even though appearing physically "normal" they are disabled personally, socially and occupationally thus requiring by rule – A Multidisciplinary and Holistic approach of management should be taken. A detailed assessment and handling every area of deficit with the collaboration of Psychiatrist, neurosurgeon, neurologist, psychologist, social worker, vocational trainer, physiotherapist and community groups, is the cornerstone in dealing with this silent epidemic i.e. TBI.

7.1 Assessment

Detailed medical, psychiatry and developmental history, neurological examination, mental status examination, quantification of neuropsychiatric symptoms using standardized inventories, neuroimaging should be done.

Role of imaging

CT SCAN is the most efficient modality in patients whose neurological status changes rapidly and detect contusions. MRI is more sensitive, especially to post traumatic non-hemorrhagic lesions and small subdural collections, preferred for contusions, diffuse axonal injury, frontotemporal lesions. Structural volumetric MRI helps in determining volumetric change in gray matter, white matter and CSF18 FDG PET measure cerebral metabolic rate corroborate with SPECT finding. SPECT is most sensitive for white matter lesions *(Bruce Lee et al, 2005).*

Role of Neuropsychological testing

Neuropsychological testing is most reliable way to document and quantify cognitive impairments. Sleep-deprived EEG helps to diagnose seizures.

Role of Neuronal markers

Various serum markers are also available to diagnose the severity of injury like NEURONAL MARKERS: Neuronal specific enolase, Cleaved tau protein Neurofilament, Ubiquitin C terminal hydroxylase L1 among GLIAL MARKERS: Glial fibrillary acid protein, S 100 B

7.2 Pharmacological management

TBI patients are sensitive to the drug treatment. Five general rules are recommended for treating TBI patients.

1. Start with lower doses and increase dosage at slower rates than those recommended for non- TBI patients.
2. Adequate therapeutic trial should be given.
3. Proper drug-drug monitoring to be done.
4. Partial responder from a drug may benefit from the addition of a second drug with a different mode of action.
5. Lower the dosage if problem worsens after treatment initiation. If problem persist, discontinue the medication (Comprehensive Textbook of Psychiatry 10th edition).

- 7.2.1 Cognitive deficits - Amantadine memantine, Methylphenidate, Bromocriptine, Donepezil, Rivastigmine, Rivastigmine (*Wheatonet al 2009, Whyte et al. 2004, Ghate et al, 2018)*.
- 7.2.2 Depressive disorder - Selective serotonin reuptake inhibitors (SSRI) (e.g., sertraline or citalopram) are generally recommended as first-line. Tricyclic antidepressants are less favorable benefit-risk profile and also lower the seizure threshold in patients with moderate-severe TBI (JR Fann et al, 2009).
- 7.2.3 Mania – Anticonvulsants such as carbamazepine or valproate may be more effective than lithium. Valproate may exacerbate cognitive impairment in some, but it appears less likely to do so than either carbamazepine or lithium (Dikmen et al.,2000). Atypical antipsychotics- risperidone, olanzaoine, ziprasidone is also found to be effective in mania.
- 7.2.4 Psychosis - Atypical antipsychotics seem to be more appropriate, dose must be half or one third of the usual ones (Schwartzbold et al 2008).
- 7.2.5 Anxiety spectrum disorder - SSRIs, buspirone and naltrexone for anxiety spectrum disorder (Sudarsanan et al, 2019).
- 7.2.6 Apathy – Psychostimulants like methylphenidate and dopamine agonist - amantadine, selegiline are found to be effective for treating apathy *(Lane et al 2009, Newburn et al,2005)*

7.3 Non pharmacological management

7.3.1 Global approaches - These aims adjusting the behavior of the patient's close circle, adapting the environment, targets the need to gain awareness of the disability and to accept it, improving emotional disturbances, integration and social interactions, rehabilitation and remediation activities, occupational therapy are dealt.

7.3.2 Specific interventions – These include behavioural and cognitive-behavioural therapies which aim to help the subject alter beliefs, thoughts and behaviors by way of a process of "cognitive restructuring and family therapy helps family members of patient in dealing with the sufferings *(Fayol P et al, 2003)*.

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